IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Edward R. LaVallie et al.		
Application No.:	08/949,904	Group Art No.:	1642
Filed:	October 15, 1997	Examiner:	Susan NMN Ungar
For:	Human SDF-5 Protein and Compositions		
Confirmation No.:	8744		
Customer No.:	22204		

Commissioner for Patents
P.O. Box 1450
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APPEAL BRIEF

As set forth in the Notice of Appeal filed October 15, 2004, Appellants hereby appeal the Examiner's final rejection of claims 18, 19, 22, 23 and 33 of the above-identified application. Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the final rejection of these claims.

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I. REAL PARTY IN INTEREST

The real party in interest is Wyeth, Five Giralda Farms, Madison, NJ 07940.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 18, 19, 22, 23 and 33 have been finally rejected and are the subject matter of this appeal. Claims 1-17, 21, 24, 26 and 27 have been withdrawn from consideration. Claims 20, 25, 28 and 29 have been canceled. Claims 30-32 have not been entered.

IV. STATUS OF AMENDMENTS

No amendment has been filed or submitted after the final rejection mailed July 16, 2004.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 18 is directed to a purified human SDF-5 polypeptide comprising the amino acid sequence depicted in SEQ ID NO:2. This claim is supported at least by page 10, lines 7-15, of the specification.

Claim 19 relates to a purified human SDF-5 protein which is produced by expressing a DNA molecule comprising the nucleotide sequence from nucleotide #316 to #1143 of SEQ ID NO:1. The SDF-5 protein thus produced comprises the amino acid sequence from amino acid #21 to amino acid #295 of SEQ ID NO:2. Claim 19 is supported at least by page 5, lines 31-35; page 8, lines 16-35; and page 9, lines 1-9 and 14-25, of the specification. The amino acid sequence from amino acid #21 to amino acid #295 of SEQ ID NO:2 is identical to SEQ ID NO:3. See the Sequence Listing of the present application.

Claim 22 relates to a purified human SDF-5 protein comprising the amino acid sequence depicted in SEQ ID NO:2. Claim 22 is supported at least by page 10, lines 7-15, of the specification.

Claim 23 is directed to a purified human SDF-5 protein comprising the amino acid sequence depicted in SEQ ID NO:3. Claim 23 is supported at least by page 10, lines 7-15, of the specification.

Claim 33 prescribes a purified human SDF-5 polypeptide comprising the amino acid sequence depicted in SEQ ID NO:3. This claim is supported at least by page 10, lines 7-15, of the specification.

VI. GROUNDS OF REJECTION

Appellants respectfully request the Board to reverse the following grounds of rejection: (1) rejection of claims 18, 19, 22, 23 and 33 under 35 U.S.C. § 101 for lack of utility; and (2) rejection of claims 18, 19, 22, 23 and 33 under § 112, first paragraph, for containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to use the invention (i.e., nonenablement).

VII. ARGUMENTS

A. Rejection Under 35 U.S.C. § 101

1. Claims 18 and 22

Claims 18 and 22 are directed to a purified human SDF-5 polypeptide or protein comprising the amino acid sequence depicted in SEQ ID NO:2. Appellants respectfully submit that a purified human SDF-5 polypeptide/protein, as recited in claims 18 or 22, can bind, at least to a reasonable probability, to the protein products of human Wnt genes. Wnt genes were known to play important roles in oncogenesis, kidney tubulogenesis and limb bud development at the time the present application was filed. See Finch *et al.*, PROC. NATL. ACAD. SCI. USA, 94:6770-6775 (1997) (Exhibit 1, hereinafter "Finch"), particularly, page 6770, left column. Therefore, the polypeptide/protein of claims 18 and 22 can be used as a Wnt protein-binding agent for the determination of the molecular basis of cancer or other diseases. The polypeptide/protein of claims 18 and 22 can also be used to isolate or purify Wnt proteins.

Example 7 of the present application (page 52, line 35, to page 53, line 26) describes that SDF-5 is expressed in the developing joints of the appendicular skeleton but not in the bones of the axial or appendicular skeleton. Accordingly, a purified human SDF-5 polypeptide/protein, as recited in claims 18 and 22, can also be used to raise antibodies for the detection of the developing joints. The ability to detect or monitor joint development or formation has important clinical applications, as joint disease is a major human health problem.

In addition, Example 7 of the present application demonstrates that SDF-5 protein, when used in combination with BMP-2, can promote cartilage differentiation *in vitro*. Accordingly, a purified human SDF-5 polypeptide/protein, as recited in claims 18 and 22, can also be used, at least to a reasonable probability, to promote cartilage formation, wound healing or tissue repair.

Based on any of the above-described utilities, Appellants respectfully submit that claims 18 and 22 satisfy the utility requirement under 35 U.S.C. § 101. See Raytheon Co. v. Roper Corp., 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. 101 is clearly shown").

Additional utilities of the instant application are set forth in the more detailed sections below, which respond to the Examiner's various statements concerning the utility of claims 18 and 22 and the subject application.

Detection and Isolation of Protein Products of Wnt Genes

As observed by the Federal Circuit in Fujikawa v. Wattanasin, 93 F.3d 1559, 39 USPQ.2d 1895 (Fed. Cir. 1996), all that is required for establishing utility under 35 U.S.C. § 101 is to provide a sufficient correlation between the data disclosed in the specification and the asserted utility so as to convince those skilled in the art, "to a reasonable probability," that the claimed subject matter will exhibit the asserted utility. See id., 93 F.3d at 1564, 39 USPQ.2d at 1899. "[T]he test results need not absolutely prove that the compound is pharmacologically active" and "[a]ll that is required is that the tests be 'reasonably indicative of the desired [pharmacological] response.'" Id. (internal citation omitted).

As noted, claims 18 and 22 are directed to a purified human SDF-5 polypeptide or protein comprising SEQ ID NO:2. As admitted by the Examiner, this purified human SDF-5 polypeptide/protein shares high sequence homology with murine SDF-5 protein, as described in Shirozu *et al.*, GENOMICS, 37:273-280 (1996) (Exhibit 2, hereinafter "Shirozu"). A comparison of SEQ ID NO:2 to murine SDF-5 protein demonstrates that both sequences have the identical cysteine-rich domain (amino acids 40-152, also known as the "CRD" domain). See page 8 of the Office Action mailed August 19, 1998 (Paper No. 7). See also the sequence comparison in the facsimile sent by the Examiner to Appellants on August 5, 1998 (Exhibit 3). The CRD domain

was known to contain a putative binding site for Wnt proteins. See Exhibit 1, Finch, page 6772, left column. In addition, one of ordinary skill in the art knew at the time the present application was filed that murine SDF-5 protein can bind to Wg, i.e., the *Drosophila* homology of human Wnt-1, and that proteins comprising CRD domains are likely to be able to interact with Wnt proteins or modulate their activities. See Exhibit 1, Finch, page 6774, right column, and page 6770, left column.

Based on the sequence homology between SEQ ID NO:2 and murine SDF-5 protein, and the fact that murine SDF-5 protein can bind to the *Drosophila* homology of human Wnt-1 protein, Appellants respectfully submit that those of ordinary skill in the art would be convinced, at least to a reasonable probability, that a purified human SDF-5 protein/polypeptide, as recited in claims 18 and 22, can bind to human Wnt proteins, such as human Wnt-1 protein. In addition, the present application explicitly asserts that a human SDF-5 protein comprising SEQ ID NO:2 retains *Frazzled* activity and, therefore, can bind to the protein products of Wnt genes. See page 4, line 26, to page 5, line 20, of the specification. See also, In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974) ("[A] specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented *must* be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter *unless* there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.") (emphasis in original).

On pages 8-11 in the Office Action mailed March 26, 2002, the Examiner contends that because even a single amino acid substitution may dramatically affect the biological activity of a protein, "no one of skill in the art would believe it more likely than not that the claimed protein is a Wnt binding protein or accept the assertion that the claimed protein is a Wnt binding protein in the absence of a consensus sequence for Wnt binding." However, as demonstrated hereinabove, the polypeptide/protein of claims 18 and 22 has the same putative Wnt-binding domain as murine SDF-5 protein, and murine SDF-5 protein was known to be able to bind to Wnt proteins (e.g., the *Drosophila* homology of human Wnt-1). See Exhibit 1, Finch, page 6774, right column. Moreover, it appears that the Examiner requires Appellants to provide absolute proof that the claimed protein/polypeptide will bind to Wnt proteins. However, absolute proof is not required for establishing utility. See Fujikawa, 93 F.3d at 1564, 39 USPQ.2d at 1899. As noted by the Federal Circuit, all that is required for establishing utility is that one of ordinary skill in

the art would believe, to a reasonable probability, that the claimed SDF-5 protein/polypeptide would bind to Wnt proteins. In view of the sequence homology between the protein/polypeptide of claims 18 and 22 and murine SDF-5 protein, and the fact that murine SDF-5 protein can bind to the *Drosophila* homology of human Wnt-1 protein, Appellants respectfully submit that one of ordinary skill in the art would believe, at least to a reasonable probability, that the protein/polypeptide of claims 18 and 22 would bind to human Wnt proteins (e.g., human Wnt-1 protein).

Over-expression of Wnt genes was known to be a causal factor for mammary hyperplasia and adenocarcinoma. See Exhibit 1, Finch, page 6770, left column. Therefore, one utility of the protein/polypeptide of claims 18 or 22 is to detect abnormalities in the expression of Wnt genes (e.g., Wnt-1 gene) in cancer patients. Appellants respectfully submit that this utility would be apparent to one of ordinary skilled in the art at the time the present application was filed, particularly in view of the asserted binding activity and the knowledge regarding the involvement of Wnt genes in oncogenesis. Consequently, an explicit description of this utility in the specification is not necessary. See In re Folkers, 344 F.2d 970, 145 USPQ 390 (CCPA 1965) (holding that a chemical compound had a utility under 35 U.S.C. § 101 even though that utility was not explicitly disclosed in the patent application, because a physico-chemical property of the compound, as recited in the application, made it apparent to one of ordinary skill that the compound was useful). Identification of abnormal expression of Wnt genes in a cancer patient not only facilitates the understanding of the molecular basis of the disease, but also allows the selection of more effective treatments for the patient (e.g., a treatment that will suppress the Wnt gene expression).

In addition, the protein/polypeptide of claims 18 or 22 can be used for affinity purification of Wnt proteins. This utility is readily apparent to one of ordinary skill in the art in view of the asserted binding activity and, therefore, an explicit description of this utility in the specification is not required. Wnt proteins purified in this fashion can be used for the preparation of antibodies or for the identification of other binding partners of Wnt proteins.

Based on all of the above reasons, Appellants respectfully submit that claims 18 and 22 satisfy the utility requirement under 35 U.S.C. § 101. Accordingly, Appellants respectfully request the Board to reverse the final rejection of claims 18 and 22.

Detection of Developing Joints

Appellants also submit that a purified human SDF-5 protein/polypeptide, as recited in claims 18 and 22, can be used to raise antibodies for labeling or detecting the developing joints of the appendicular skeleton. This further utility is readily apparent to one of ordinary skill in the art, particularly in view of Example 7 of the present application. Example 7 illustrates that SDF-5 is expressed in the developing joints of the appendicular skeleton but not in the bones of the axial or appendicular skeleton. Therefore, an antibody specific to human SDF-5 protein can be used to detect joint development or monitor skeleton formation *in vivo* or *in situ*. This utility allows one to investigate prenatal or postnatal death caused by bone developmental diseases. Examples of such bone developmental diseases include, but are not limited to, skeletal dysplasias and osteochondrodysplasia, as appreciated by those skilled in the art at the time the present application was filed. Antibodies specific to human SDF-5 proteins are described on page 10, lines 27-33, of the specification.

Based on the foregoing, Appellants respectfully submit that claims 18 and 22 further satisfy the utility requirement under 35 U.S.C. § 101. Accordingly, reversal of the final rejection of these claims is respectfully requested.

Cartilage Formation and Tissue Repair

Appellants further submit that a purified human SDF-5 protein/polypeptide, as recited in claims 18 and 22, can be used to promote cartilage formation, wound healing, or tissue repair. As also demonstrated in Example 7 of the present application, murine SDF-5, when used in combination with BMP-2, increases cartilage phenotype in MLB13MYC-clone 14 cells. As is known in the art, MLB13MYC-clone 14 is a representative cell line for skeletal progenitor cells, which can differentiate into chondroblasts or osteoblasts. See page 1761, right column, of Rosen *et al.*, J. BONE AND MINERAL RESEARCH, 9:1759-1768 (1994) (Exhibit 4, hereinafter "Rosen"). See also, page 4033, right column, of Banerjee *et al.*, ENDOCRINOLOGY, 142:4026-4039 (2001) (Exhibit 5, hereinafter "Banerjee"). Because of the high sequence identity between murine SDF-5 and human SDF-5, as specifically noted by the Examiner in Exhibit 3, Appellants respectfully submit that one of ordinary skill in the art would readily be convinced that human SDF-5 protein,

when used in combination with BMP-2, can also increase cartilage phenotype *in vitro*. Moreover, Appellants submit that the present application provides a sufficient correlation between the *in vitro* data and the contemplated *in vivo* use of the claimed protein/polypeptide for cartilage formation, wound healing, or tissue repair. See Fujikawa, 93 F.3d at 1565, 39 USPQ.2d at 1900 ("[A] 'rigorous correlation' needs not be shown in order to establish practical utility; 'reasonable correlation' suffices").

The *in vivo* utility of the claimed human SDF-5 protein/polypeptide for cartilage formation, wound healing or tissue repair is asserted at numerous places in the specification. See, e.g., page 7, lines 10-11 and 32-35; page 8, lines 1-3; and page 19, lines 13-16 and 29-32. Appellants respectfully submit that these assertions "*must* be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter *unless* there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." In re Langer, 503 F.2d at 1391, 183 USPQ at 297 (CCPA 1974) (emphasis in original).

With reference now to the Final Office Action mailed July 16, 2004, on page 3 the Examiner states that "a review of the literature using the STN:Bioscience Database Group which comprises greater than 64 databases, including both the US Patent Database as well as the US Published Application Database, does not reveal a single hit based on a search of MLB13MYC-clone 14 cells that would suggest that a direct nexus or correlation can be drawn between the *in vitro* responsiveness of these cells and effectiveness for treatment in the *in vivo* condition." However, the present application does not claim using MLB13MYC-clone 14 cells to treat *in vivo* conditions. Instead, claims 18 and 22 are directed to a purified human SDF-5 protein/polypeptide. As discussed hereinabove, the present application asserts that human SDF-5 protein can be used, at least to a reasonable probability, to stimulate cartilage formation *in vivo*. This utility does not necessarily depend on the use of MLB13MYC-clone 14 cells. Rather, as appreciated by those of ordinary skill in the art, other skeletal or cartilage precursor cells can be used for cartilage formation or tissue repair *in vivo*. The use of MLB13MYC-clone 14 cells in Example 7 is to demonstrate that human SDF-5 protein, when used in combination with BMP-2, can promote cartilage formation *in vitro* and, therefore, is likely to have the same effect *in vivo*. See Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985) ("[*I*]*n vitro* results with respect to the particular pharmaceutical activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing

procedures of the pharmaceutical industry would not be as they are"). Based on the above reasons, Appellants respectfully submit that the rationale underlying the Examiner's review of the literature is misplaced and, therefore, does not provide a reason for one skilled in the art to question the objective truth of the utility set forth in the present application.

Additionally, on page 3 of the Final Office Action, the Examiner further contends that the increase in the expression of proteins involved in cartilage formation is not significant because "the specification clearly omits the term 'significant' when discussing the increase of the mRNA compared to BMP-2 alone," and that such an increase is "so small that applicant is not even sure that it is there." The Examiner, however, does not provide any objective evidence to support his contention. Moreover, the specification nowhere suggests that the term "increase" should be construed as "decrease," "no change", or "no significant change." Instead, the specification unambiguously states that "[t]his effect is similar to that previously observed for combinations of PTHrP and BMP-2, except there seems to be a greater enhancement of cartilage phenotype with the SDF-5 combination." See page 53, lines 24-26, of the specification. See also, Cross, 753 F.2d at 1048-1049, n17, 224 USPQ at 746, n17 ("Variation in potency, moreover, is a matter of degree of activity, . . . but is still indicative of activity") (internal citation omitted); and Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571, 24 USPQ.2d 1401, 1412 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"). Based on all of these reasons, Appellants respectfully submit that the Examiner's contention with respect to the meaning of the term "increase" is unfounded and, therefore, does not provide a reason for one skilled in the art to question the objective truth of the utility set forth in the present application.

On page 4 of the Final Office Action, the Examiner added that "cartilage markers were not demonstrated to be increased, rather mRNA encoding said markers were shown to be increased and for the reasons of record, additional work must be done in order to determine how to use the claimed invention." However, protein synthesis from mRNA is the central dogma of molecular biology. The Examiner appears to challenge this central dogma by alleging that an increased level of mRNA cannot be reasonably correlated to an increased level of protein. The Examiner's contention is, accordingly, contrary to the belief of one of ordinary skill in the art at the time the present application was filed and, therefore, does not provide a reason for one skilled in the art to question the objective truth of the utility set forth in the present application.

On page 5 of the Final Office Action, the Examiner further alleges that "the specification does not teach the levels of increase required for the use of instant invention, does not teach that levels of increase are sufficient to in fact alter cartilage formation compared to BMP-2 administration alone . . .." However, as described in Example 6 of the specification (page 52, lines 14-33), bone and cartilage cells have different expression markers, and Example 7 demonstrates that treatment of MLB13MYC clone 14 cells with SDF-5 and BMP-2 suppresses the expression of bone markers while increasing the expression of cartilage markers. Appellants respectfully submit that these findings sufficiently support the stimulating effect of the combination of SDF-5 and BMP-2 on cartilage formation. The fact that the exact level of increase or decrease is not disclosed does not negate this stimulating effect. Moreover, Example 7 is directed to a pharmaceutical activity of SDF-5 (i.e., its stimulating effect on cartilage formation when used in combination with BMP-2), but not to the use of MLB13MYC clone 14 cells for cartilage formation or tissue repair. Based on all of the above reasons, Appellants respectfully submit that the fact that the present invention does not teach the exact or precise level of increase/decrease required for cartilage formation does not provide a reason for one skilled in the art to question the objective truth of the utility set forth in the present application.

On page 5 of the Final Office Action, the Examiner also contends that "the claimed invention is an undeveloped art." However, the Examiner does not present any evidence that would suggest that the use of stimulating factors to promote cartilage formation or tissue repair was an undeveloped art at the time the present application was filed. In the Office Action mailed April 27, 1999, the Examiner did cite Dermer, BIO/TECHNOLOGY, 12:320 (1994) (Exhibit 6, hereinafter "Dermer"), and Freshney, CULTURE OF ANIMAL CELLS: A MANUAL OF BASIC TECHNIQUE (1st ed., 4, Alan R. Liss, Inc., 1983, New York, p.4) (Exhibit 7, hereinafter "Freshney"), to support the contention that there are many differences between cultured cells and their counterparts *in vivo*. However, Dermer and Freshney relate to cancer studies or *in vitro* cultures in general. They are not relevant to the art that involves the use of stimulating factors to promote cartilage formation or tissue repair.

Appellants respectfully submit that the use of stimulating factors to promote cartilage formation or tissue repair was not an undeveloped or unpredictable art at the time the present application was filed. For instance, Rosen (Exhibit 4) states that "[t]he availability of morphogenic molecules, such as BMP-2, allows us to control the differentiation of progenitor

cells to osteoblasts and chondroblasts in both settings in vivo and in vitro." See page 1766, right column, of Exhibit 4 (emphasis added). For another instance, Gilbert, THE AMERICAN JOURNAL OF KNEE SURGERY, 11:42-46 (Winter, 1998) (Exhibit 8, hereinafter "Gilbert"), states that "Sellers et al recently demonstrated that recombinant human bone morphogenic protein-2 (rhBMP-2) can accelerate the healing of full-thickness defects of articular cartilage." See page 45, left column, of Exhibit 8. "Sellers et al" refers to an animal study published in 1997. See page 46, left column, of Exhibit 8. For still another instance, the present application refers to PCT Publication WO84/01106 for wound healing and related tissue repair. See page 19, lines 29-32, of the specification. With reference to Example 5 of WO84/01106 (Exhibit 9), a well-established *in vivo* protocol for testing the effects of stimulating factors on tissue repair is described therein. Based on all of these reasons, Appellants respectfully submit that the use of stimulating factors to promote cartilage formation or tissue repair does not involve an unpredictable or undeveloped art and, therefore, the Examiner has failed to provide a reason for one skilled in the art to question the objective truth of the utility set forth in the present application.

On pages 6-8 of the Final Office Action, the Examiner also contends that the present application does not provide a nexus between "*in vitro* experimentation and efficacy of *in vivo* treatment." However, Rosen explicitly states that "[t]he availability of morphogenic molecules, such as BMP-2, allows us to control the differentiation of progenitor cells to osteoblasts and chondroblasts in both settings in vivo and in vitro." See page 1766, right column, of Rosen (Exhibit 4, emphasis added). In addition, inventor Edward R. LaVallie expressly states in his declaration (Exhibit 10) that "[t]he increase in cartilage markers in Example 7 demonstrates that SDF-5, in combination with BMP-2, is involved in the regulatory pathway for the formation of cartilage" and that "[t]he use of SDF-5 in combination with BMP-2 to increase cartilage formation is a credible utility." See page 2 of Exhibit 10. Edward R. LaVallie also states that "the *in vitro* data as set forth in the instant patent specification reasonably supports applications *in vivo*." See id.

Moreover, Appellants respectfully submit that 35 U.S.C. § 101 only demands a reasonable correlation, as opposed to a rigorous nexus, between *in vitro* data and the contemplated *in vivo* use. See Fujikawa, 93 F.3d at 1565, 39 USPQ.2d at 1900 ("[A] 'rigorous correlation' needs not be shown in order to establish practical utility; 'reasonable correlation'

suffices"). "[A]dequate proof of any pharmacological activity constitutes a showing of practical utility" and "a therapeutical utility is not necessarily synonymous to a pharmaceutical activity." Cross, 753 F.2d at 1049-1050, 224 USPQ at 746-747. Appellants believe that the present application sufficiently demonstrates, at least to a reasonable degree, that the claimed human SDF-5 protein possesses an *in vivo* pharmacological activity, i.e., the stimulating effect on cartilage formation when used in combination with BMP-2.

This *in vivo* utility of the instant invention is similar to that upheld by the Federal Circuit in Cross, where the application at issue described imidazole derivatives that possess an inhibitory action for thromboxane synthetase in human or bovine platelet microsomes. A platelet microsome is an *in vitro* milieu including blood platelets and other granular elements of protoplasm. Thromboxane synthetase is an enzyme which leads to the formation of thromboxane A[2], which was postulated, at the time the application at issue was filed, to be a causal factor in platelet aggregation. Platelet aggregation is associated with several deleterious conditions in mammalian, such as platelet thrombosis, pulmonary vasoconstriction or vasospasm, inflammation, hypertension, and collagen-induced thrombosis.

The application at issue in Cross, however, did not provide any *in vivo* testing results that would show the effectiveness of the claimed compounds in treating any of the deleterious conditions associated with thromboxane A[2]. Moreover, the Cross application disclosed that the inhibitory effect of structurally similar compounds was not satisfactory and had not been put to practically therapeutic use. Despite the lack of *in vivo* data, applicant Iizuka asserted that the description of the *in vitro* utility was sufficient to comply with the practical utility requirement of 35 U.S.C. § 101. The Federal Circuit agreed, stating that "adequate proof of any pharmacological activity constitutes a showing of practical utility" and "a therapeutical utility is not necessarily synonymous to a pharmaceutical activity." Cross, 753 F.2d at 1049-1050, 224 USPQ at 746-747.

The court further stated:

> *In vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* test results. Moreover, *in vitro* results with respect to the particular pharmaceutical activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Iizuka has not urged, and rightly so, that there is an invariable exact correlation between *in*

> *vitro* test results and *in vivo* test results. Rather, Iizuka's position is that successful *in vitro* testing for a particular pharmaceutical activity establishes a significant probability that *in vivo* testing for this particular pharmacological activity will be successful.

Id., 753 F.2d at 1050, 224 USPQ at 747.

In addition, the Federal Circuit observed that Iizuka's expert witness testified that "he would expect that *in vivo* testing of the imidazole derivatives of the phantom count would show that these compounds also possessed an inhibitory action for thromboxane synthetase, i.e., there would be a reasonable correlation between *in vitro* test results and *in vivo* test results." Cross, 753 F.2d at 1050, 224 USPQ at 747. The court found that this evidence was sufficient to establish a practical utility. See id.

As in Cross, the *in vitro* testing described in Example 7 of the present application demonstrates that the combination of SDF-5 and BMP-2 promotes cell differentiation that favors cartilage formation. The declaration by Edward R. LaVallie explicitly states that "[a]s one of skill in the art, I believe that the *in vitro* data as set forth in the instant patent specification reasonably supports applications *in vivo*." See page 2 of Exhibit 10. Accordingly, Appellants respectfully submit that the present application provides a reasonable correlation between the *in vitro* data and the corresponding *in vivo* activity. See Cross, 753 F.2d at 1050-1051, 224 USPQ at 747-748 ("[A] rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence" and "[s]uccessful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility"). See also, Fujikawa, 93 F.3d at 1565, 39 USPQ.2d at 1900 ("Of course, it is possible that some compounds active in vitro may not be active in vivo. But, as our predecessor court in Nelson explained, a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); and In re Brana, 51 F.3d 1560, 1567, 34 USPQ.2d 1436, 1442 (Fed. Cir. 1995) ("[O]ne who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans").

Furthermore, Appellants respectfully submit that a nexus between *in vitro* data and "efficacy" of *in vivo* treatment is not required by 35 U.S.C. §101. "Title 35 does not demand that

such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." In re Brana, 51 F.3d at 1567, 34 USPQ.2d at 1442. The requirements for a patent should not be confused with the requirements for obtaining government approval to market a particular drug for human consumption. See id.

Based on all of the above reasons, Appellants respectfully submit that the Examiner has failed to present any reason for one skilled in the art to question the objective truth of the utility set forth in the present application – namely, the use of SDF-5 in combination of BMP-2 to promote cartilage formation, wound healing or tissue repair. In addition, Appellants respectfully submit that the present application provides a reasonable correlation between the *in vitro* data and the *in vivo* use of SDF-5 protein. Accordingly, Appellants respectfully request that the Board reverse the final rejection of claims 18 and 22.

2. Claims 23 and 33

Claims 23 and 33 are directed to a purified human SDF-5 protein or polypeptide comprising the amino acid sequence depicted in SEQ ID NO:3, which is identical to SEQ ID NO:2 except that SEQ ID NO:3 lacks the first twenty amino acid residues of SEQ ID NO:2. These first twenty amino acid residues are predicted to form a signal peptide. See page 5, lines 26-31, of the specification. Therefore, the protein/polypeptide of claims 23 and 33 is expected to be an active species of human SDF-5 protein. See page 5, lines 33-35, of the specification.

For the same reasons set forth above in connection with claims 18 and 22, Appellants respectfully submit that the protein/polypeptide of claims 23 and 33 can bind, at least to a reasonable probability, to the protein products of human Wnt genes. Accordingly, the protein/polypeptide of claims 23 and 33 can be used as a Wnt protein-binding agent for the detection of abnormalities in the expression of Wnt genes (e.g., Wnt-1 gene) in cancer patients. The protein/polypeptide of claims 23 and 33 can also be used for affinity purification of Wnt proteins. Wnt proteins thus purified can be used to prepare antibodies or to identify other binding partners of Wnt proteins.

Moreover, for the same reasons set forth above, the protein/polypeptide of claims 23 and 33 can be used to raise antibodies for detecting or monitoring joint development or formation.

This allows one to investigate prenatal or postnatal death caused by bone developmental diseases.

Furthermore, like the protein/polypeptide of claims 18 and 22, the protein/polypeptide of claims 23 and 33, when used in combination of BMP-2, can enhance, at least to a reasonable probability, cartilage formation, wound healing or tissue repair *in vivo*. The correlation between this contemplated *in vivo* use and the *in vitro* data of Example 7 was apparent to one of ordinary skill in the art at the time the present application was filed, particularly in view of the numerous assertions in the present application (e.g., page 7, lines 10-11 and 32-35; page 8, lines 1-3; and page 19, lines 13-16 and 29-32) and the knowledge of those skilled in the art at the time the present application was filed (e.g., Exhibits 4 and 5). See also, the declaration by Edward R. LaVallie (Exhibit 10); Cross, 753 F.2d at 1050, 224 USPQ at 747 ("[*I*]*n vitro* results with respect to the particular pharmaceutical activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween"); and Fujikawa, 93 F.3d at 1565, 39 USPQ.2d at 1900 ("[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices").

All of the above-described utilities for the protein/polypeptide of claims 23 and 33 are either explicitly described in the specification, or obvious to those of ordinary skill in the art in view of the written description of the present application. Based on the foregoing, Appellants respectfully submit that claims 23 and 33 also satisfy the utility requirement under 35 U.S.C. § 101. Reversal of the final rejection of claims 23 and 33 is, therefore, respectfully requested.

3. Claim 19

Finally, claim 19 is directed to a purified human SDF-5 protein produced by expressing a DNA molecule comprising #316 to #1143 of SEQ ID NO:1 in cultured cells. The protein thus produced comprises the amino acid sequence from amino acid 21 to amino acid 295 of SEQ ID NO:2. This amino acid sequence is identical to SEQ ID NO:3. As discussed above, the protein/polypeptide of claims 23 and 33 also comprises SEQ ID NO:3.

Because the protein/polypeptide of claims 23 and 33 satisfies the utility requirement, Appellants respectfully submit that the protein of claim 19 also satisfies the utility requirement.

Accordingly, Appellants respectfully request the Board to reverse the final rejection of claim 19 under 35 U.S.C. § 101.

B. Rejection Under 35 U.S.C. § 112, First Paragraph

1. Claims 18 and 22

As discussed above, a purified human SDF-5 protein/polypeptide of claims 18 or 22 can bind to Wnt proteins and, therefore, can be used for the detection or isolation of the protein products of Wnt genes. Methods for detecting a protein of interest using a binding agent were well known in the art at the time the present application was filed. Exemplary methods include cell assays, such as that described on page 6774, right column, of Finch (Exhibit 1) (citing Ratter *et al.*), or immunocytochemistry. The latter method can be achieved, for example, by incubating a fluorescence-labeled SDF-5 protein with tissue slices, or by first incubating a ligand-conjugated SDF-5 protein with tissue slices and then detecting any bound SDF-5 protein using an agent capable of recognizing the conjugated ligand. All of these methods were well known in the art at the time the present application was filed and, therefore, would not require undue experimentation. See Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) ("[A] patent need not teach, and preferably omits, what is well known in the art"). Based on the foregoing, Appellants respectfully submit that the present application enables one skilled in the art to use the protein/polypeptide of claims 18 and 22 and, therefore, claims 18 and 22 satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. Accordingly, Appellants respectfully request that the Board reverse the final rejection of claims 18 and 22 for nonenablement.

As discussed above, the protein/polypeptide of claims 18 or 22 can also be used for affinity purification of Wnt proteins. The Wnt proteins thus purified can be used to make antibodies, or to identify binding partners of Wnt proteins. Methods for affinity purification of a protein of interest using a binding agent were well known in the art at the time the present application was filed. Exemplary methods include affinity chromatography. Accordingly, Appellants respectfully submit that the present application further enables one skilled in the art to use the protein/polypeptide of claims 18 and 22 and, therefore, claims 18 and 22 satisfy the

enablement requirement under 35 U.S.C. § 112, first paragraph. Reversal of the final rejection of claims 18 and 22 for nonenablement is, therefore, respectfully requested.

In addition, as discussed above in connection with the many utilities of the instant invention, the protein/polypeptide of claims 18 or 22 can be used to raise antibodies for detecting or monitoring joint development or formation. Methods suitable for this purpose were well known in the art at the time the present application was filed. Exemplary methods include immunohistochemistry. Accordingly, Appellants respectfully submit that the present application further enables one skilled in the art to use the protein/polypeptide of claims 18 and 22 and, therefore, claims 18 and 22 satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. Reversal of the final rejection of claims 18 and 22 is, therefore, respectfully requested.

As discussed above, the protein/polypeptide of claims 18 or 22 can also be used to promote cartilage formation, wound healing or tissue repair *in vivo*. Methods suitable for this purpose were also well known in the art at the time the present application was filed. Exemplary methods include those described in Example 5 of WO84/01106 (Exhibit 9), which was cited in the specification. See page 19, lines 29-32, of the specification. On pages 12-13 of the Final Office Action, the Examiner contends that "it has not been established that the *in vitro* cell line is correlative for the instantly suggested utility of the claimed invention or for the treatment of any disease." However, as discussed at length hereinabove, the present application does indeed provide a sufficient correlation between the *in vitro* pharmaceutical activity described in Example 7 and the contemplated *in vivo* use, particularly in light of the declaration by Edward R. LaVallie (Exhibit 10) and Exhibits 4 and 5 attached hereto, which reflect the knowledge of one of ordinary skill in the art at the time the present application was filed. In addition, as observed by the Federal Circuit, "*in vitro* results with respect to the particular pharmaceutical activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween." Cross, 753 F.2d at 1050, 224 USPQ at 747. See also Fujikawa, 93 F.3d at 1565, 39 USPQ.2d at 1900 ("Of course, it is possible that some compounds active in vitro may not be active in vivo. But . . . a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"). Appellants respectfully submit that these assertions by the Federal Court equally apply to 35 U.S.C. § 112, first paragraph, and that the enablement requirement requires only a "reasonable" correlation, as opposed to an "absolute" correlation,

between *in vitro* data and *in vivo* use. A contrary holding would render the utility requirement moot. Based on all of these reasons, Appellants respectfully submit that the present application provides sufficient guidance for those skilled in the art to use the protein/polypeptide of claims 18 and 22 *in vivo* and, therefore, claims 18 and 22 satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. Accordingly, Appellants respectfully request that the Board reverse the final rejection of claims 18 and 22

2. Claims 23 and 33

As discussed in considerable detail hereinabove, the protein/polypeptide of claims 23 and 33 has the same utilities as the protein/polypeptide of claims 18 and 22. Because claims 18 and 22 are enabled, Appellants respectfully submit that claims 23 and 33 are also enabled at least for the many reasons set forth above. Reversal of the final rejection of claims 23 and 33 is, therefore, respectfully requested.

3. Claim 19

As discussed above, the protein prescribed by claim 19 comprises SEQ ID NO:3 and, therefore, has the same utilities as the protein/polypeptide of claims 23 and 33. Because claims 23 and 33 are enabled, Appellants respectfully submit that claim 19 is also enabled at least for the many reasons set forth above. Reversal of the final rejection of claim 19 is, therefore, respectfully requested.

Conclusion

Since the Examiner's final rejection under 35 U.S.C. § 101 and § 112, first paragraph, is inappropriate for the reasons set forth above, Appellants respectfully request the Board to reverse each ground of rejection.

Respectfully submitted,

Date: February 7, 2005

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VIII. CLAIM APPENDIX

Claims Involved in the Appeal

18. A purified human SDF-5 polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

19. A purified human SDF-5 protein produced by the steps of
    a) culturing a cell transformed with a DNA molecule comprising the nucleotide sequence from nucleotide #316 to #1143 as shown in SEQ ID NO: 1; and
    b) recovering and purifying from said culture medium a protein comprising the amino acid sequence from amino acid #21 to amino acid #295 as shown in SEQ ID NO: 2.

22. A purified human SDF-5 protein comprising the amino acid sequence from amino acid #1 to #295 of SEQ ID NO: 2.

23. A purified human SDF-5 protein comprising the amino acid sequence from amino acid #1 to #275 of SEQ ID NO: 3.

33. A purified human SDF-5 polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

XI. EVIDENCE APPENDIX

Exhibit 1: Finch *et al.*, PROC. NATL. ACAD. SCI. USA, 94:6770-6775 (1997), which was submitted by Appellants in the Information Disclosure Statement filed January 16, 1998, and discussed on page 7 of the Office Action mailed March 26, 2002 (Paper No. 28).

Exhibit 2: Shirozu *et al.*, GENOMICS, 37:273-280 (1996), which was cited and discussed on pages 7-9 of the Office Action mailed August 19, 1998 (Paper No. 7).

Exhibit 3: The sequence comparison provided by the Examiner to Appellants in a facsimile dated August 5, 1998.

Exhibit 4: Rosen *et al.*, J. BONE AND MINERAL RESEARCH, 9:1759-1768 (1994), which was submitted by Appellants in the Information Disclosure Statement filed September 18, 2003, and discussed on pages 5-6 of the Office Action mailed July 16, 2004.

Exhibit 5: Banerjee *et al.*, ENDOCRINOLOGY, 142:4026-4039 (2001), which was submitted by Appellants in the Information Disclosure Statement filed April 14, 2004, and discussed on pages 6-7 of the Office Action mailed July 16, 2004.

Exhibit 6: Dermer, BIO/TECHNOLOGY, 12:320 (1994), which was cited on page 3 of the Office Action mailed April 27, 1999 (Paper No. 12), and discussed on pages 7-8 of the Office Action mailed November 12, 2003 (Paper No. 42).

Exhibit 7: Freshney, CULTURE OF ANIMAL CELLS: A MANUAL OF BASIC TECHNIQUE (1st ed., 4, Alan R. Liss, Inc., 1983, New York, pp. 4-6), which was cited on page 3 of the Office Action mailed April 27, 1999 (Paper No. 12), and discussed on pages 8-9 of the Office Action mailed November 12, 2003 (Paper No. 42).

Exhibit 8: Gilbert, THE AMERICAN JOURNAL OF KNEE SURGERY, 11:42-46 (Winter, 1998), which was submitted by Appellants in the Information Disclosure Statement filed April 14, 2004, and discussed on page 12 of Appellants' Response filed May 12, 2004, in reply to the Office Action mailed November 12, 2003.

Exhibit 9: PCT publication WO84/01106, which was discussed on page 19, line 31, of the specification.

Exhibit 10: The declaration by Edward R. LaVallie pursuant to 37 C.F.R. § 1.132, which was filed by Appellants on May 12, 2004, and was discussed on page 2 of the Office Action mailed July 16, 2004.

X. RELATED PROCEEDINGS APPENDIX

There are no related appeals or interferences.